CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
TRIETHYLENE GLYCOL

Chemical Code: 596, Tolerance #: 50483

Original: April 25, 2002

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, studies inadequate, no adverse effects indicated
Chronic toxicity, dog:	Data gap, no study submitted
Oncogenicity, rat:	Data gap, no study submitted
Oncogenicity, mouse:	Data gap, no study submitted
Reproduction, rat:	Data gap, no study submitted.[Publication from the open literature was reviewed with no adverse effect]
Teratology, rat:	Data gap, no study submitted.
Teratology, mouse:	Data gap, studies inadequate, no adverse effects indicated
Teratology, rabbit:	Data gap, no study submitted.
Gene mutation:	Data gap, no study submitted
Chromosome effects:	Data gap, no study submitted
DNA damage:	Data gap, no study submitted
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
All record numbers through 132347 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T020425
Original: Kishiyama and Gee, April 25, 2002

Triethylene glycol is used as an antimicrobial in air sanitizers with little agricultural use in California.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

50483 - 006 132322 Fitzhugh, O. G. and Nelson, A. A. "Comparison of the Chronic Toxicity of Triethylene Glycol with That of Diethylene Glycol." (Publ. In: *Journal of Industrial Hygiene and Toxicology*, 28 (2): 40 - 43, March, 1946.) Triethylene glycol and diethylene glycol were compared for toxicity at concentrations of 0, 1, 2, and 4 per cent when fed for 2 years in the diet of 12 Obsborne-Mendel male rats/group beginning as weanlings. Diethylene glycol retarded body weight, increased the incidence of bladder stones and tumors, and caused chronic damage to the liver and kidneys. NOEL not determined. Triethylene glycol treatments showed no toxic effects under study conditions. NOEL > 4% of the diet. UNACCEPTABLE (numerous deficiencies). Supplemental information . (Kishiyama and Gee, 4/10/02).

50483 - 006 132341 Robertson, O. H., Loosli, C. G., Puck, T. T., Wise, H., Lemon, H. M., and Lester Jr., W. "Tests for the Chronic Toxicity of Propylene Glycol and Triethylene Glycol on Monkeys and Rats by Vapor Inhalation and Oral Administration." (University of Chicago and U.S. Army Epidemiological Board. Published in an unknown journal, pages 52 - 76, received June 5, 1947.) Propylene glycol was tested with rats and monkeys by inhalation and triethylene glycol by inhalation and oral ingestion, also with rats and monkeys. Propylene glycol vapor at 0.17 - 0.35 mg/l to rats and at 0.10 - 0.22 and 0.23 - 0.35 mg/l to monkeys; triethylene glycol vapor at 0.0025 - 0.005 mg/l to rats and 0.002 - 0.003 and 0.0031 - 0.0046 mg/l to monkeys and triethylene glycol by ingestion at 0.14 - 2.66 cc/kg for rats and at 0.5 (3 and 5.5 months), 0.25 (12 months) and 0.5 (12 and 14.5 months) cc/day/kg for monkeys were evaluated for toxicity. Exposure time varied from 1 to 18 months, apparently with exposure for 24 hours per day. The atmospheres were supersaturated with either glycol, forming a fog, at the higher exposures. The number of animals per group varied and the distribution by sex was not always given. Rats were allowed to breed during the experiment and gave birth while under exposure, so that the number of animals per group varied. Body weight of female rats was not recorded because of pregnancies. The text states that the reproduction of rats appeared normal. Under study conditions, propylene glycol vapor was not deleterious to monkeys and rats, and similarly for triethylene glycol vapor. Blood cell counts were comparable to controls at all doses by inhalation and oral ingestion. There was no treatment-related pathology in rats. Mortality of monkeys was due primarily to disease rather than toxicity of treatment. Reduced weight gain in monkeys may have been due to food availability and content. Rat and monkeys showed no deleterious effects from triethylene glycol ingestion. Only limited parameters for hematology, urinalysis and histopathology apparently were investigated. UNACCEPTABLE. Not upgradeable. Supplemental information. (Kishiyama and Gee, 4/15/02).

No record number. Van Miller, J. P. and B. Ballantyne "Subchronic peroral toxicity of triethylene glycol in the Fischer 344 rat." (Union Carbide, publ. in *Vet. Human Toxicol.* 43 (5), 269 - 276, 2001) Triethylene glycol (TEG, >99%) was fed in the diet to Fischer 344 rats for 90 days at 0, 10000, 20000 or 50000 ppm. There were 30/sex in the control and high dose groups and 20/sex in the low and mid-dose groups. Ten per sex in the control and high dose groups were fed untreated diet for 6 weeks following dosing for a recovery period. There were no clinical signs, ophthalmological effects, biologically significant findings in hematology or clinical chemistry. Urine volume was increased and pH decreased at 50000 ppm at the end of the 13-week dosing period but no after the recovery period. Body weight and weight gain were lower at 50000 ppm in both sexes, the effect being greater with males. There was some recovery of the weight difference in males following dosing termination. Although there were some absolute organ weight differences

following dosing but not after recovery. There were no gross necropsy or histological findings, according to the text (no data). There were no adverse effects from treatment. UNACCEPTABLE (summary data only in a publication). Upgradeable with the full study including individual data. (Gee, 4/25/02)

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted

ONCOGENICITY, MOUSE

No study submitted

REPRODUCTION, RAT

No record number. Bossert, N. L., Reel, J. R., Lawton, A. D., George, J. D. and Lamb IV, J. C. "Reproductive toxicity of triethylene glycol and its diacetate and dimethyl ether derivatives in a continuous breeding protocol in Swiss CD-1 mice." (National Toxicology Program, NIEHS, and Research Triangle Park, publ. in *Fundamental and Applied Toxicology* 18, 602 - 608 (1992)) Triethylene glycol (97% with 2.6% diethylene glycol) was administered in drinking water at 0.3, 1.5 or 3% for 98 days to 20 breeding pairs of CD-1 mice with 40 pairs in the control group. For males, this was equivalent to 0, 0.59, 3.30 and 6.78 g triethylene glycol per kg body weight. Dose selection was based on a preliminary trial with 8/sex/group given 0, 1, 2.5, 5, 7.5 or 10% (w/v) for 2 weeks. Mortality occurred at 5% and above. For the main study, summary data only were presented for the number fertile/number cohabited, the mean number of litters/pair, live pups per litter, proportion born alive and the mean live pup weight. All parameters were equivalent except for mean pup weight which was statistically significantly lower than the concurrent control group for the 1.5% and 3% groups, being 1.60 and 1.59 g versus 1.65 g for 1.5%, 3% and controls, respectively. Other control groups in the study, however, had mean weights of 1.61 and 1.65 g. The text also states that, when the F1 for 3% were raised to adults and mated, the mean pup weights determined on days 0, 21 and 74 of the F2 litters were comparable to controls (no data shown). The effect on F1 pup weight, therefore, was not flagged. Organ weights of F1 offspring were comparable except for liver, which was higher in both sexes at 3% compared with controls (the only two groups investigated). Results with the diacetate were similar with a transient effect on pup body weight at 3%. The dimethyl ether, however, was toxic to reproduction. Triethylene glycol was evaluated overall as not demonstrating reproductive toxicity. Supplemental data. (Gee, 4/18/02)

TERATOLOGY, MOUSE

50483 - 006 132338 Schuler, R. L., B. D. Hardin, R. W. Niemeier, G. Booth, K. Hazleden, V. Piccirillo, and K. Smith. "Results of Testing Fifteen Glycol Ethers in a Short-Term *In Vivo* Reproductive Toxicity Assay." (Published in: *Environmental Health Perspectives* 57, pp. 141-146 (1984)). Fifteen glycol ethers were administered by gavage to 50 pregnant mice/compound during gestation days 7 through 14. Triethylene glycol (99%) was given at a dose of 11270 mg/kg. There was 4% maternal mortality compared with none in the control. There was 100% litter viability to day 3. Neonatal pup weight was 1.5 g* compared with 1.6 g for

control but weight gain days 1 -3 was comparable (1.0 g versus 0.9 in the control). There were 9 pups per litter compared with 10 per litter in the concurrent controls. No further analysis of pups was reported. Ethylene glycol monoethyl ether at 1400 mg/kg resulted in no viable litters. Ethylene glycol (EG) at 11090 mg/kg resulted in 15/37 (41%) viable litters with a mean of 2 live pups per litter compared with 9 in the control. Mean pup weight with EG was 1.4 g* compared with 1.7 g in controls. A NOEL could not be established for any compound tested as only one dose was given. The purpose was to screen compounds for potential adverse reproductive effects for further testing. Supplemental information. (Kishiyama and Gee, 4/12/02)

50483 - 006 132340 Hardin, B. D., Schuler, R. L., Burg, J. R., Booth, G. M., Hazelden, K. P., MacKenzie, K. M., Piccirillo, V. J. and Smith, K. N. "Evaluation of 60 Chemicals in a Preliminary Developmental Toxicity Test. " (Publ. in *Teratogenesis, Carcinogenesis, and Mutagenesis* 7:29-48 (1987)). Ethylene glycol at 11090 mg/kg, ethylene glycol monomethyl ether at 1400 mg/kg, and triethylene glycol at 11270mg/kg were administered daily via gavage during gestation days 6 through 13 to 50 mated CD-1 female mice/treatment group. Triethylene glycol did not cause any significant effects on pups. Ethylene glycol and ethylene glycol monomethyl ether were reported positive for developmental toxicity. Both chemicals caused intrauterine death, reduced litter size and fetal weight, and maternal mortality. UNACCEPTABLE. Supplemental information. (Kishiyama and Gee, 4/15/02).

NOTE: The data for triethylene glycol in this publication appear to be the same as in record no. 132338 but with more details.

TERATOLOGY, RAT

No study submitted.

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

No study submitted

CHROMOSOME EFFECTS

No study submitted

DNA DAMAGE

No study submitted.

NOTE: An abstract appeared in *The Toxicologist* 15: 82 (1995) in which the authors, J. S. Vergnes and B. Ballantyne, Bushy Run Research Center, state that triethylene glycol was negative in the Ames test and the CHO/HGPRT assay, the sister chromatid assay and an *in vitro* assay for chromosome aberrations. None of these studies has been submitted. For filling the data gaps, the full reports are needed. (Gee, 4/25/02).

NEUROTOXICITY

Not required at this time.

MISCELLANEOUS STUDIES, NOT REQUIRED UNDER SB-950

50483 - 006 132324 Latven, A. R. and Molitor, H. "Comparison of the toxic, hypnotic and irritating properties of eight organic solvents." (Merck Institute, publication in an unidentified journal, pages 89 - 94, received 6/3/38, submitted by RegWest Company for the CSMA Glycols Joint Venture, in 1994). Triethylene glycol, stated as pure, was one of the solvents tested in white mice, 4/group, by the intravenous, subcutaneous and oral routes at 6 doses. Animals were observed periodically for a week following an acute dose. Solvents were given undiluted. The table of data included: subcutaneous: LD0 (8.0 cc/kg), LD50 (8.75 cc/kg), LD100 (10.0 cc/kg) and max. nonsymptomatic dose (8.0 cc/kg); oral: LD0 (14.0 cc/kg), LD50 (18.5 cc/kg), LD100 (24.0 cc/kg), max. nonsymptomatic dose (6.0 cc/kg); and intravenous: LD0 (5.0 cc/kg), LD50 (6.5 cc/kg), LD100 (8.0 cc/kg), max. nonsymptomatic dose (2.0 cc/kg). Symptoms were evaluated as present when 1/4 mice placed on a 1 cm. wide ledge showed dizziness. Irritant properties were tested by instillation of 0.5 cc into one eye of a rabbit with 5 tests being done and eye effects observed at 4 and 24 hours. Triethylene glycol rated "+" for edema and hyperemia. Intradermal injection of 0.1 cc into the shaved abdomen of guinea pigs and redness, ulceration, etc., recorded with triethylene glycol receiving a "++" rating. Legs of frogs were immersed in solvents with 0.1N HCl as control and the time between immersion and reflex retraction recorded. The control was 0.8 sec (mean of 15 frogs) and triethylene glycol, 2.7 seconds. There was no irritation of intact skin of rabbits. Propylene glycol was less toxic than triethylene glycol of those solvent s tested [70% alcohol, 95% alcohol, carbitol, diacetin, ethylene glycol, ethyl lactate, glycerol, propylene glycol and triethylene glycol]. No worksheet. Supplemental data. (Gee, 4/10/02).

50483 - 006 132328 *Food and Cosmetics Toxicology* 17, Supplement, 913 - 916, December, 1979. "Monographs on fragrance raw material." The pages include a summary of acute, subacute and chronic information with citations. The acute data includes the LD50 for several species by the oral, iv, ip, dermal, and subcutaneous routes. For inhalation, 1 ppm was without effects on monkeys or rats. Humans exposed to 0.5 - 1 ppm showed no ill effects [Harris, T. M. and Stokes, J. *Am. J. Med. Sci.* 209, 152 (1945)]. It is an eye and skin irritant but not a sensitizer. Some of the references cited were not submitted to the Department for review. These include a study in which rats were given subcutaneous injections of 1, 2 or 4 ml/kg for 4 weeks with no gross signs of toxicity but showed inflammation at the injection site of 4 ml/kg and some blood aberrations and all treated rats had increase in blood urea nitrogen. This same publication [Stenger, E. G. *et al., Arzneimittel-Forsch.* 18: 1536, 1968] also reported on dogs given iv injections of 9.1 or 0.5 ml/kg for 4 weeks. Animals showed no signs of "poisoning" but more showed "flattened wpithelial cells" in urine than controls and thrombophlebitis at the injection site. See document for details. No worksheet. (Gee, 4/12/02)

50438 - 006 132339 Guillot, J. P., M. C. Martini, J. Y. Giauffret, J. F. Gonnet and J. Y. Guyot. "Safety evaluation of some humectants and moisturizers used in cosmetic formulations." (Publ. in *International Journal of Cosmetic Science* 4: 67 - 80 (1982)) Triethylene glycol was one of a series of compounds tested for eye and skin irritation potential. Concentrations used were 100 and 10% in water. Result for the acute ocular irritation index in rabbits with 100 % triethylene glycol was 11.33, ranked as slight irritation. For primary cutaneous irritation with rabbits, the score was 0.08 or non-irritant. The mean maximum cutaneous index was 0.42 for 100 % (well tolerated) and 0.07 for 10% (very well tolerated). Details of methodology were not described. No worksheet. Supplemental data. (Gee, 4/15/02).

50483 - 006 132342 McKennis Jr., H., R. A. Turner, L. B. Turnbull, E. R. Bowman, W. W. Muelder, M. P. Neidhardt, C. L. Hake, R. Henderson, H. G. Nadaeu and S. Spencer "The excretion and metabolism of triethylene glycol." (Medical College of Virginia, Dow Chemical Company and Olin Mathieson, publ. in *Toxicology and Applied Pharmacology* 4: 411 - 431 (1962)) Male albino rats were given a single oral dose of triethylene glycol-C-14 (22.5 mg to rats weighing

112 to 145 g) and excretion in the air, urine and feces measured. At the end of a 5-day period, 91 - 98% of the dose was recovered. Approximately 90% appeared in the urine, 1% in air and 1 - 5% in the feces. Most expired in the air was recovered in the first 12 hours and in the first day in the urine. Most of the material excreted was unchanged triethylene glycol. A female rabbit given 200 mg/kg single dose, excreted 34.3% as parent material. Both species excreted some oxidized metabolite(s). The high degree of excretion in the urine was interpreted as consistent with the low or limited toxicity of triethylene glycol. Much of the publication was devoted to methodology for the preparation and purification of derivatives of triethylene glycol and quantitation. No worksheet. Supplemental data. (Gee, 4/16/02).

50483 - 006 132343 Karel, L., B. H. Landing and T. S. Harvey "The intraperitoneal toxicity of some glycols, glycol ethers, glycol esters, and phthalates in mice." (Toxicology and Pathology Sections, Edgewood Arsenal, MD, publ. in *J. Pharmaol. Exp. Therap.* 90: 338 - 347, 1947) A series of 16 compounds were investigated with triethylene glycol being one. Groups of 10 female Carworth Farms mice were given intraperitoneal injections of undiluted materials and observed for 7 days. The objective was to determine the LD50 and examine animals for gross and microscopic pathological changes. For triethylene glycol, the LD50 was 7.24 ml/kg, 8.15 g/kg (sp. gr. 1.125) or 54.27 millimoles/kg. The highest dose giving 0 mortality in the first 24 hours was 5.34 ml/kg and the lowest dose giving 100% mortality during the 7 days was 7.98 ml/kg. Pathological changes during days 1 - 4 following a single dose were reported as toxic reaction in the spleen and thymus with "severe" lesions, mild renal glomerular and tubular damage and mild pulmonary congestion, high white count and atelectasis. Examination on days 5 - 7 showed only mild regeneration of spleen and lymphoid tissue with no other lesions. No worksheet. Supplemental data. (Gee, 4/16/02).

50483 - 006 132344 Smyth, Jr., H. F., J. Seaton and L. Fischer "The single dose toxicity of some glycols and derivatives." (Publ. in *Journal of Industrial Hygiene and Toxicology* 23 (6): 259 - 268 (1941)) Commercial grades of a large series of compounds were tested to determine the LD50 of 50% (1 ml contained 0.5 gm of test article) in water using male Wistar rats and male and female guinea pigs. Triethylene glycol was tested at 50% maximum concentration. The LD50 was 22.06 g/kg (19.38 to 25.13, 95% certainty) in rats and 14.66 g/kg (13.75 to 15.70) in guinea pigs. No other data were presented. No worksheet. Supplemental data. (Gee, 4/16/02)

50438 - 006 132345 Lauter, W. M. and V. L. Vrla "Toxicity of triethylene glycol and the effect of para-amino-benzene-sulfonamide upon toxicity of this glycol." (Publ. in *Journal of the American Pharmaceutical Association 29:* 5 - 8 (1940) Albino rats were given commercial grade triethylene glycol at a number of doses and dilutions over 30 days with a 15 day post-treatment period. The sex distribution was not always stated, although a comment was made about litters being produced. In another series, young rats (28 - 34 grams body weight) were dosed. In the first series, 5/group (sex unknown), were dosed by gavage as follows: 0.1 ml/kg (5% aqueous solution), 3.0 ml/kg (30% aqueous solution), 10 and 20 ml/kg, undiluted. At 10 ml/kg, all survived the dosing and post-treatment periods but showed some toxic symptoms including loss of hair and diarrhea. At the lower doses, all survived and appeared "normal" and some females produced litters. At 20 ml/kg, all died within 48 hours of treatment initiation. The lethal dose was concluded to be between 10 and 15 ml/kg undiluted material. At 5% aqueous solution by volume in drinking water, 3/5 adults died by 28th day and 2 survived but all showed severe toxic symptoms. At 10% by volume to adults, 5/5 were dead by day 12. For young rats, no signs were seen at 3% by volume. At 5% by volume, 1/5 died on 15th day and severe signs were seen in the first 2 weeks of dosing with slow weight gain followed by improvement in weight and behavior (no details). Adult rats survived doses of 1 and 0.75 g/kg p-amino-benzene-sulfonamide in triethylene glycol as solvent. Five rats/group were given intramuscular injections of triethylene glycol of 5, 7.5 and 10 ml/kg (equivalent to 5.6, 8.4 and 11.3 g/kg). At 8.4 g/kg, 3/5 died and all died at 11.3 g. Estimated M.L.D. was 8.4 g/kg body weight. No worksheet. Supplemental data. (Gee,

4/16/02).

50483 - 006 132346 Pages on triethylene glycol from a volume by V. K. Rowe and M. A. Wolf with no title or reference identified. A brief review of uses, properties and toxicity of triethylene glycol. No original data. No worksheet. Supplemental information. (Gee, 4/16/02)

50438 - 006 132347 Pages 61 to 63 from an unidentified source reviewing toxicological considerations of a series of glycols, including triethylene glycol. No worksheet. Supplemental information. (Gee, 4/16/02).